REMARKS

With entry of this amendment, claims 1, 3, 5 and 7-11 are pending in the application. Reconsideration is requested.

Applicants thank Examiner Baskar for her courtesy and consideration in the telephonic examiner interview held on August 25, 2004 with the undersigned. Changes to claim language to overcome the objections and the 35 USC § 103 rejections were discussed. The substance of the interview is reflected in the claim amendments, and in the remarks below.

The disclosure was objected to for lack of complete information. Amendment to the specification has been made to include information about the biological deposit. Claims 2, 4 and 6 have been cancelled. Claims 1, 3 and 5 have been amended to include the limitations thereof, and to recite the specific sequence SEQ ID NO:2. Claims 1, 3 and 5 have also been formally amended to overcome objections to the wording. No new matter has been added.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-11 were rejected under 35 U.S.C. §112, first paragraph, as failing to provide an enabling disclosure without complete evidence that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of biological materials. The specification has been amended to insert the deposit information. A statement from one of the inventors attesting to the fact that the deposited material is the same as that described in the application in included with this filing. Applicants confirm that upon the granting of a patent, the deposit will be freely available to the public without restrictions and that the deposit will be maintained for the required period of not less than 30 years or 5 years beyond the date of the last request for a sample was made. In addition, the ATCC receipt for the deposit made under the Budapest Treaty is enclosed. Withdrawal of the rejection is accordingly requested.

Claim objections

Claims 3 and 5 were objected to because of the wording. The claims have been amended

in accordance with the Examiner's helpful suggestions, both in the office action and in the telephonic examiner interview. Withdrawal of the objection is respectfully requested..

Rejections under 35 U.S.C. § 103

Claims 1-11 stand rejected under 35 U.S.C. §103 as being unpatentable over Kumar et al. or Chang et al. in view of Genton et al. According to the Examiner's position, Kumar teaches a vaccine composition comprising recombinant *P. falciparum* MSP-1_{42}, FVO strain and Freund's adjuvant and a method of inducing an immune response to recombinant MSP-1_{42} in Aotus monkeys by injecting recombinant protein in Freund's adjuvant. The Examiner further states that Chang et al. teach a vaccine composition comprising a recombinant baculovirus 42 KD protein, i.e. MSP-1_{42} from *P. falciparum*, FUP strain and complete Freund's adjuvant. The Examiner also states that in both cases, sera from immunized monkeys were incubated with parasites to show production of effective protection.

It is the Examiner's position that it would be obvious to a person of skill in the art to combine either Kumar or Chang with Genton et al., who teach the use of adjuvant B in a blood stage malaria vaccine that includes MSP 1 and MSP 2 from *P. falciparum* 3D7 to obtain the present invention. This rejection is traversed for the following reasons.

The presently amended claims recite a malaria vaccine comprising *P. falciparum* 3D7 MSP-1_{42} derived from *E. coli* (SEQ ID NO:2) and expressed as a soluble protein such that it retains its native folding. An important feature of the present invention is the expression of the antigen in a native functional form that is capable of inducing a substantial level of protective immunity.

Kumar et al. evaluated two different antigens, an *E. coli* GST-MSP-1_{42} fusion protein and a 19 kD yeast-expressed fragment, which causes some confusion for interpreting the results. These antigens are both derived from the FVO strain of *P. falciparum*. The MSP-1_{42} portion of the GST-MSP-1_{42} fusion protein is the one that is most similar to the presently used protein from the 3D7 strain but is about 50% different in primary structure especially in the N-terminal two thirds of the molecule. In addition, the GST-MSP-1_{42} fusion protein of Kumar contains

approximately 200 additional amino acids that come from GST, and increases the molecular weight by about 25 kD. The substantial difference in the two proteins leads to different outcomes in purification strategy, and in the resulting functionality of the product as a vaccine. The *E. coli* fusion protein of Kumar was not purified in a way that would lead to a protein that was properly stabilized by disulfide bridges, as in the present invention. Kumar et al. discloses a composition that includes a GSP fusion with an antigen from MSP-42 that is purified and eluted with reduced glutathione. No further description of the purification is provided, and in particular, nothing that would lead to the required disulfide bridges that are necessary for the functionality of the present invention. The antibody titers reported by Kumar et al. in response to their disclosed vaccine are substantially lower than the levels that are achieved by the present invention using a regimen that contains a lower amount of active substance. This can be seen by comparing the values in Table 1 of Kumar et al. with the values reported in of the present specification in Table 6 at page 69. Because of the form in which the data is presented, this comparison can be made only indirectly owing to differences in the species vaccinated (Kumar, Aotus monkeys; present invention, humans), dose (Kumar 200 μg/dose; present invention 50 μg/dose) and adjuvant (Kumar, Freund's Adjuvant, which is the most potent immunological adjuvant known; present invention, ASO2A, which is an adjuvant that is useful for human application and is significantly less potent than Fruend's). Despite these differences the current invention induced at least 5 times higher ELISA reactive $MSP1_{42}$ –specific antibodies than did the GST-$MSP\text{-}1_{42}$ fusion protein from Kumar. Our direct comparisons show that Aotus monkeys vaccinated with the present invention in Freund's adjuvant produced about 300 times more antibodies that those vaccinated with the present invention in AS02A. Thus the inherent immunogenicity of the current invention is about 1000 times greater than the GST-$MSP\text{-}1_{42}$ fusion protein of Kumar.

Finally, it is particularly noted that after comparing the GST-$MSP\text{-}1_{42}$ fusion protein and the $MSP1_{19}$ protein vaccines, Kumar rejected the GST-$MSP\text{-}1_{42}$ fusion protein as a vaccine that lacked potency in favor of the $MSP1_{19}$ protein vaccine.

Thus, the presently claimed vaccine differs from Kumar et al. in at least the following

ways:

1. The primary structure of FVO (Kumar) is approximately 50% different from the primary structure of 3D7 (the present invention);

2. The protein of Kumar is not expressed as a recombinant soluble protein from *E. coli* that retains its native structure.

3. The protein of Kumar is not purified in a way that would lead to proper stabilization by disulfide bridges; and

4. The antibody titers reported by Kumar et al. are much lower than those achieved with the presently claimed vaccine.

The Examiner has relied upon Genton et al. for teaching the use of Adjuvant B in a malaria vaccine (see page 8, first full paragraph, of the Office Action). However, Genton et al. does not remedy the deficiency of Kumar et al. to disclose a vaccine comprising an MSP-1_{42} protein SEQ ID NO:2 that is expressed as a soluble protein from *E. coli*, as presently claimed. It is respectfully submitted that if Genton et al. had been combined with Kumar as proposed by the Examiner, it would have resulted a vaccine that comprised the fusion protein as taught by Kumar et al., and not the MSP-1_{42} protein that is expressed as a soluble protein from *E. coli* that retains its native structure of the presently claimed vaccine. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Chang et al. discloses a baculovirus recombinant polypeptide based on *P. falciparum* MSP-1 derived from the FUP isolate, and isolated by affinity chromatography. It is respectfully submitted that Chang et al., like Kumar et al., does not teach or suggest a vaccine comprising *P. falciparum* MSP-1_{42} as set forth in SEQ ID NO:2 that is expressed in *E. coli* as a soluble protein. For the reasons presented above, Genton et al. does not remedy this deficiency. The combination of Chang et al. with Genton et al. will result in a vaccine comprising a baculovirus recombinant peptide as taught by Chang et al., and not the MSP-1_{42} protein that is expressed as a soluble protein from *E. coli* that retains its native structure of the presently claimed vaccine.

The Examiner stated in the current Office Action that the rejection had not been overcome because "claims 1, 3 and 5 ... do not recite the limitation "strain 3D7". The claims

have been amended to be limited to this strain, specifically to SEQ ID NO:2. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3 and 5 have been rejected as being indefinite. It is the Examiner's position that the expression "expressed as a soluble protein" is indefinite. The Examiner suggests that the claim should read "expressed to produce a soluble protein". Applicants respectfully disagree. Proteins are properly "expressed", not "expressed to produce". The antecedent subject for this phrase is "C-terminal 42 kD fragment of merozoite surface protein-1 from *P. falciparum* CD7", which does not "produce" a soluble protein, but is "expressed as a soluble protein". Withdrawal of the rejection is accordingly requested.

All objections and rejections having been addressed, it is respectfully requested that the rejections be withdrawn and a Notice of Allowance issued. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is hereby invited to telephone the undersigned at the number provided.

Respectfully submitted,

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